Claims

1. A method of predicting the receptor-modulating activity of a compound which modulates the biological activity of a receptor which comprises:

(a) providing a panel comprising a plurality of members, said members differing in their ability to bind to said receptor depending on which of a plurality of different reference conformations the receptor is in, where the effect of a plurality of reference substances, known to modulate the biological activity of the receptor, on the binding of each member of the panel is known, and is characterized as a reference fingerprint for each such reference substance;

(b) screening a test substance of unknown activity relative to said receptor to determine its effect on the binding of each member of said panel to said receptor, thereby obtaining a test fingerprint for said test substance,

(c) comparing the test fingerprint to the reference fingerprints, and

(d) predicting the biological activity of the test substance, based on the assumption that its biological activity will be similar to that of reference substances with similar fingerprints.

2. The method of claim 1 where the effect of reference substances on the binding by said panel members is determined by

(a) providing a panel comprising a plurality of members, said members differing in their ability to bind to said receptor depending on which of a plurality of different reference conformations the receptor is in, and

(b) screening a plurality of reference substances known to modulate the biological activity of said receptor to determine their effect on the binding of each member of said panel to said receptor, thereby obtaining a reference fingerprint for each reference

substance, said fingerprint comprising a plurality of panel-based descriptors, each panel-based descriptor characterizing the effect of the reference substance on the binding of a particular panel member to said receptor, said reference fingerprint's panel based descriptors collectively characterizing the effect of the reference substance on the binding of all of the panel members, individually, to said receptor.

3. The method of claim 2 where said panel members are obtained by a method which comprises:

(a) providing one or more ligands for the receptor;

(b) screening a first combinatorial library comprising a plurality of members for the ability to bind to a receptor in at least two different reference conformations, including at least one ligand-bound conformation, and

(c) based on said screening, providing a panel of first library members, said panel comprising members which differ with respect to their ability to binding to the receptor, depending on its conformation.

4. The method of claim 1 in which at least one reference conformation is an unliganded conformation of the receptor.

5. The method of claim 3 in which said panel comprises at least two (i), (ii) and (iii) below:

(i) at least one member which binds the ligand-bound receptor more strongly than it binds the unliganded receptor, and which detectably binds the unliganded receptor,

(ii) at least one member which binds the ligand-bound receptor less strongly than it binds the unliganded receptor, and

(iii) at least one member which binds the ligand-bound receptor about as strongly as it binds the unliganded receptor, and detectably binds both.

6. The method of claim 1 wherein a plurality of different ligands are used in characterizing the panel.

7. The method of claim 1 in which the biological activity

of the reference substances at said receptor is known for a plurality of different tissues, so that the biological activity of the test substance in said tissues is predicted.

8. The method of claim 1 in which the receptor is a nuclear receptor.

9. The method of claim 1 in which the receptor is an estrogen receptor (ER).

10. The method of claim 1 in which the receptor is a G-protein coupled receptor, a G protein, or a G protein subunit.

11. The method of claim 1 in which at least one ligand is a pharmacological agonist or antagonist of the receptor.

12. The method of claim 1 in which at least one conformation is induced by a natural ligand of the receptor.

13. The method of claim 1 in which at least one conformation is induced by a ligand which is not a natural ligand of the receptor.

14. The method of claim 1 in which the first combinatorial library is an oligopeptide library.

15. The method of claim 1 in which the first combinatorial library is a nucleic acid library.

16. The method of claim 1 in which the test substances are provided and screened in the form of a combinatorial library.

17. The method of claim 1 in which the biologically active component of said test substance is an organic compound with a molecular weight of less than 500 daltons.

18. The method of claim 1 in which screening steps (a), (d) and (e) are performed in vitro.

19. The method of claim 1 in which screening steps (a), (d) and (e) are performed in a cell-based assay which is not an assay of a whole multicellular animal or tissues and organs isolated from such an animal.

20. The method of claim 19 in which screening steps (d) and (e) are performed in a two-hybrid assay system, and the members of the panel are peptides.

21. The method of claim 1 in which the receptor is a glucocorticoid receptor.

22. The method of claim 9 in which at least one reference substance is selected from the group consisting of estradiol, estriol, nafoxidine, 4-OH tamoxifen, clomifene, premarin, raloxifene, ICI 182,780, 16α-OH estrone, and progesterone.

23. The method of claim 8 in which at least one panel member is a peptide comprising Leu-Xaa-Xaa-Leu-Leu.

24. The method of claim 9 in which at least one panel member has a substantially higher affinity for ERα than for ERβ, and at least one other panel member has a substantially higher affinity for ERβ than for ERα.

25. The method of claim 9 in which at least one panel member binds the receptor substantially more strongly when the receptor is bound to estradiol then when the receptor is not so bound.

26. The method of claim 9 in which at least one panel member binds the receptor substantially less strongly when the receptor is bound to estradiol when it is not so bound.

27. The method of claim 9 where said panel comprises

(1) at least one member with a substantially higher affinity for ERβ than for ERα, whose affinity is substantially greater for estradiol-bound ER than for unliganded ER;

(2) at least one member with a substantially higher affinity for ERα than for ERβ, whose affinity is substantially the same for estradiol-bound ER and for unliganded ER;

(3) at least one member with a substantially higher affinity for ERα than for ERβ, whose affinity is higher for estradiol-bound ERα than for unliganded ERα, and substantially the same for estradiol-bound ERβ and unliganded ERβ;

(4) at least one member with a higher affinity for ERα than for ERβ, whose affinity is substantially lower for estradiol bound ERα than for unliganded ERα, and substantially the same for estradiol-bound ERβ and unliganded ERβ; and

(5) at least one member with a substantially higher affinity for ERβ than for ERα, and whose affinity is substantially lower for estradiol-bound ER than for unliganded ER.

28. The method of claim 8 where said panel comprises at least one peptide of Table 3.

29. The method of claim 8 where said panel comprises at least one peptide from each of classes 1-5 of Table 3, or a peptide of the same class which is markedly identical to at least one of the tabulated peptides.

30. A peptide selected from the group consisting of

(1) a peptide with a substantially higher affinity for ERβ than for ERα, whose affinity is greater for estradiol-bound ER than for unliganded ER;

(2) a peptide with a substantially higher affinity for ERα than for ERβ, whose affinity is substantially the same for estradiol-bound ER and for unliganded ER;

(3) a peptide with a substantially higher affinity for ERα than for ERβ, whose affinity is substantially higher for estradiol-bound ERα than for unliganded ERα, and substantially the same for estradiol-bound ERβ and unliganded ERβ;

(4) a peptide with a substantially higher affinity for ERα than for ERβ, whose affinity is substantially lower for estradiol bound ERα than for unliganded ERα, and substantially the same for estradiol-bound ERβ and unliganded ERβ; and

(5) a peptide with a substantially higher affinity for ERβ than for ERα, and whose affinity is substantially lower for estradiol-bound ER than for unliganded ER.

31. A panel comprising peptides from a plurality of different numbered classes of peptides according to claim 30.

32. The peptide of claim 30, selected from the group consisting of the peptides of classes 1-5 of Table 3, or a peptide of the same class which is markedly identical to at least one of said peptides.

33. The peptide of claim 30, selected from the group consisting of the peptides of classes 1-5 of Table 3.

34. A non-naturally occurring peptide comprising an LXXLL motif, said peptide inhibiting tamoxifen partial agonist activity.

35. The method of claim 9 wherein said reference conformations include a plurality of conformations selected from the group consisted of unliganded receptor, estradiol-liganded receptor, 4-OH tamoxifen liganded receptor, estriol-liganded receptor, nafoxidene-liganded receptor, clomifene-

liganded receptor, premarin-liganded receptor, raloxifene-liganded receptor, ICI 182,780-liganded receptor, 16α-OH estrone-liganded receptor, and progesterone-liganded receptor.

36. The method of claim 9 where said panel comprises members representing a plurality of classes selected from the group consisting of ERα/βI, ERα/βII, ERα/βIII, ERα/βIV, ERαI, ERαII, ERαIII, ERβI, ERβII and ERβIII.

37. The method of claim 9 which distinguishes among 4-OH tamoxifen, nafoxidene, clomiphene and ratoxifene.

38. The method of claim 1 in which the conformations comprise a first liganded conformation induced by a first ligand and a second liganded conformation induced by a second and different ligand.

39. The method of claim 1 where screening step (b) is carried out in vitro.

40. A non-naturally occurring peptide selected from the group consisting of Table 10 peptides α/βI, α/βII, α/βIII, α/βIV, α/βV, αI, αII, αIII, βI, βII and βIII, or peptides markedly identical to at least one of said Table 10 peptides.

41. A non-naturally occurring peptide according to claim 40, selected from the group consisting of Table 10 peptides α/βI, α/βII, α/βIII, α/βIV, α/βV, αI, αII, αIII, βI, βII and βIII.

42. A panel comprising a plurality of different peptides according to claim 41.

43. The method of claim 8 wherein at least one member of the panel is a Table 10 peptide α/βI, α/βII, α/βIII, α/βIV, α/βV, αI, αII, αIII, βI, βII and βIII, or peptides having the same characterizing binding activity against reference conformations of ER, and markedly identical to at least one of said Table 10 peptides.

44. A non-naturally occurring peptide selected from the group consisting of

(a) the ERα binding peptides of Table 7,

(b) the ERα binding peptides of Table 8,

(c) the ERβ binding peptides of Table 9, and

(d) peptides markedly identical to a peptide of (a), (b) or (c) above.

45. The method of claim 8 in which at least one panel member is a peptide

(a) the ERα binding peptides of Table 7,

(b) the ERα binding peptides of Table 8,

(c) the ERβ binding peptides of Table 9, and

(d) peptides markedly identical to a peptide of (a), (b) or (c) above.

46. The method of claim 1 where screening step (b) is carried out in a yeast two-hybrid cell-based assay.

47. The method of claim 1 where screening step (b) is first carried out in vitro, and at least one member active in vitro is subsequently assayed for in vivo activity.

48. The method of claim 47 wherein the in vivo assay is carried out in a yeast two-hybrid assay system.

49. The method of claim 46 which employs a first hybrid comprising LexA and a second hybrid comprising B42.

50. The method of claim 1 where said screening comprises assaying the effect of said member in vivo in a mammalian two-hybrid cell-based assay.

51. The method of claim 50 where said screening employing a first hybrid comprising the yeast transcription factor Gal4 DNA binding domain and a second hybrid comprising VP16.

52. The method of claim 51 in which the screening employs HepG2 cells.

53. The method of claim 1 where said screening employs a fluorescence assay.

54. The method of claim 53 where said fluorescence assay is a time-resolved fluorescence assay.

55. The method of claim 8 in which the nuclear receptor is the progesterone receptor.

56. The method of claim 8 in which the receptor is the thyroid receptor beta.

57. The method of claim 1 in which at least one member of said panel was identified by screening for binding to a first nuclear receptor, but is subsequently used to characterize the ability of reference and test substances to bind in the presence of said member to a second and different nuclear receptor.

58. The method of claim 9 in which at least one reference receptor conformation is a tamoxifen-activated estrogen receptor and at least one member of the panel is a peptide which does not require AF-2 (helix 12) of the receptor for binding thereto.

59. A peptide which binds a ligand activated estrogen receptor and does not require AF-2 (helix 12) of the receptor for binding thereto.

60. The peptide of claim 59 in which the ligand is tamoxifen.

61. The peptide of claim 59 in which the ligand is estradiol.

62. The peptide of claim 59 which is αII, α/βIII or α/βV, or is markedly identical to at least one of said reference peptides.

63. The peptide of claim 59 which is αII, or is at least markedly identical to αII.

64. A non-naturally occurring peptide which substantially interferes with ER-mediated transcriptional activity by binding to the ER, said peptide comprising a plurality of LXXLL motifs, but said peptide not being substantially identical to any naturally occurring coactivator of ER.

65. The peptide of claim 64, where the said motifs are joined by a linker which is substantially identical to an active site-linking subsequence of a coactivator of ER.

66. The peptide of claim 65 where said coactivator sequence is the sequence of GRIP-1 which joins NR box 2 to NR box 3.

67. The peptide of claim 66, further comprising a sequence immediately prior to said LXXLL motif, such that, if the first L is numbered zero,

(1) there is a serine at -2 and a positively charged amino acid at -1, or

(2) there is a proline at -1 and a hydrophobic residue at -1, or

(3) there is a serine or threonine at -2 and a hydrophobic residue at -1.

68. The peptide of claim 67 where said hydrophobic

residue is leucine or isoleucine.

69. The peptide of claim 67 which is of type (2) and where said hydrophobic residue is leucine, and there is a histidine at -3.

70. The method of claim 8 in which the receptor is the androgen receptor.

71. The method of claim 8 in which at least one reference receptor where the ligand is selected from the group consisting of flutamide, RU486, dihydrotestosterone, cyproterone acetate, megasterol, and androsterone.

72. The method of claim 8 in which at least one reference substance is selected from the group consisting of flutamide, RU486, dihydrotestosterone, cyproterone acetate, megasterol, and androsterone.

73. A method of antagonizing the activation of a nuclear receptor in a cell which comprises exposing the cell to an antagonizing amount of a non-naturally occurring peptide comprising an LXXLL motif.

74. The method of claim 73 in which the receptor is an estrogen receptor.

75. The method of claim 73 in which the receptor is an androgen receptor.

76. The method of claim 73 in which the activation antagonized by said peptide is by estradiol.

77. A method of inhibiting AF-2 mediated ER activity, but not AF-1 mediated ER activity, in a subject, which comprises antagonizing the activation of the AF2 function of ER in the subject by the method of claim 73.

78. A method of screening for an agonist of a receptor requiring a co-activator, where the coactivator natively associated with that receptor is not known, which comprises incubating potential agonist with said receptor in the presence, sequentially or simultaneously, with each member of a panel of peptides, each member comprising an LXXLL motif, said members interacting differently with different receptor, but each member being capable of coactivating at least one known receptor.

79. A method of screening for ligands specific to ERβ

which comprises assaying for ligands which compete with peptide #293, or an ERβ specific peptide markedly identical to peptide #293, for binding to ERβ.

80. A non-naturally occurring peptide selected from the group consisting of the peptides of Table 100A, and peptides markedly identical to a peptide of Table 100A which comprise an LXXLL motif and bind estrogen receptor.

81. The method of claim 9 in which at least one member of said panel is a peptide selected from the group consisting of the peptides of Table 100A, and peptides markedly identical to a peptide of Table 100A which comprise an LXXLL motif and bind estrogen receptor.

82. A non-naturally occurring peptide selected from the group consisting of the peptides of Table 101, and peptides markedly identical to a peptide of Table 101 which comprise an LXXLL motif and bind estrogen receptor.

83. The method of claim 9 in which at least one member of said panel is a peptide selected from the group consisting of the peptides of Table 101, and peptides markedly identical to a peptide of Table 101 which comprise an LXXLL motif and bind estrogen receptor.

84. A method of identifying an oligomeric molecule which modulates the activity of a G protein coupled receptor which comprises:

screening a first combinatorial library comprising a plurality of oligomeric molecule members for the ability to bind to a G-alpha subunit in a manner specific to the activation state of the G-alpha subunit.

85. A method of identifying an oligomeric molecule which modulates the activity of a G protein coupled receptor which comprises:

screening a first combinatorial library comprising a plurality of oligomeric molecule members for the ability to bind to a G-alpha subunit in a manner indifferent to the activation state of the G-alpha subunit.

86. A non-naturally occurring peptide which binds a G-alpha in an activation-state specific manner.

87. The peptide of claim 86 which is a D-peptide that

binds the G-alpha substantially more strongly in its GDP-bound (inactive) conformation than in its GTP-bound (active) conformation.

88. The peptide of claim 86 which is a T-peptide that binds the G-alpha substantially more strongly in its GTP-bound (active) conformation than in its GDP-bound (inactive) conformation.

89. A non-naturally occurring peptide which is an I-peptide that binds a G-alpha subunit in both its GDP-bound (inactive) and GTP-bound (active) conformations with substantially the same affinity.

90. A method of identifying a modulator of a GPCR which comprises assaying potential modulators for increasing or decreasing the level of activation of said GPCR relative to its level of activation in the presence of a peptide which binds a compatible G-alpha in an activation state specific manner.

91. The method of claim 90 which comprises identifying agonist activity on said GPCR, resulting in the binding of GTP to an associated G-alpha subunit, by detecting the binding of a labeled T-peptide to said GTP-bound G-alpha subunit.

92. The method of claim 90 which comprises identifying antagonist activity on said GPCR by incubating said GPCR with an antagonist, and then detecting the increase in the level of binding of a labeled T-peptide to said GTP-bound G-alpha subunit which occurs as a result of the addition of a tagonist, and its action on said GPCR and G alpha subunit.

93. The method of claim 90 which comprises identifying agonists by permitting a labeled D-peptide to interact with an inactive G-alpha/GDP complex, exposing the GPCR to a potential agonist, whose agonist activity will activate the GPCR, and cause the conversion GDP:G-alpha to GTP:G-alpha, whereupon the labeled D-peptide dissociates, and detecting the decrease in the signal in close proximity to the GPCR.

94. The method of claim 90 which comprises identifying antagonists by first activating a G protein coupled receptor, thereby causing formation of the active G-alpha/GTP complex, and then permitting the potential antagonist to deactivate the GPCR and detecting the binding of a labeled D-peptide to the

resulting inactive G-alpha/GDP complex.

95. The method of claim 90 wherein the peptide is selected from the group consisting of (a) the peptides of Table 202B, and T-peptides markedly identical to at least one peptide of Table 202B; and (b) the peptides of Table 202C, and D-peptides markedly identical to at least one peptide of Table 202C.

96. The peptide of claim 87 which is selected from the group consisting of the peptides of Table 202B, and T-peptides markedly identical to at least one peptide of Table 202B.

97. The peptide of claim 87 which is selected from the group consisting of the peptides of Table 202C, and D-peptides markedly identical to at least one peptide of Table 202C.

98. The peptide of claim 89 which is selected from the group consisting of (a) the peptides of Table 202A, and I-peptides markedly identical to at least one peptide of Table 202A.

99. The method of claim 10 wherein at least one member of the panel is selected from the group consisting of (a) the peptides of Table 202B, and T-peptides markedly identical to at least one peptide of Table 202B; (b) the peptides of Table 202C, and D-peptides markedly identical to at least one peptide of Table 202C; (c) the peptides of Table 202A, and I-peptides substantially identical to at least one peptide of Table 202A.

100. The method of claim 2 in which the reference and test substances are screened by an in vitro assay.

101. The method of claim 2 in which the reference and test substances are screened by a cell-based assay.

102. A method of identifying a substance as an agonist or antagonist of a G-protein coupled receptor which comprises

(a) providing a cell which co-expressed (i) G-protein-coupled receptor (GPCR), (ii) a first fusion protein comprising a G-alpha subunit which interacts with said GPCR, and a first reporter protein moiety, and (iii) a second fusion protein comprising a G-alpha subunit activation-specific binding peptide according to claim 86, and a second reporter protein moiety,

(b) exposing said cell to said substance,

(c) where said agonist or antagonist activity results in a change in the level of activation of said GPCR, and hence a chance in the level of binding of said second fusion protein to said first fusion protein, said binding bringing said reporter protein moieties into sufficient proximity so as to reconstitute reporter protein activity, and

(d) detecting the signal produced by said reporter protein.

103. The method of claim 102 where the method is used to detect agonists of the GPCR, and the activation-specific peptide is a T-peptide which binds the GTP-bound (active) form of the G-alpha subunit substantially more strongly than the GDP-bound form.

104. The method of claim 102 where the method is used to detect antagonists of the GPCR, the activation-specific peptide is a D-peptide which substantially more strongly binds the GDP-bound (inactive) form of the subunit than the GTP bound form, and the cell is also exposed to a subsaturating amount of a known antagonist for said GPCR.

105. The method of claim 103 in which the T-peptide is a peptide of Table 202B or is markedly identical thereto.

106. The method of claim 104 in which the D-peptide is a peptide of Table 202C or is markedly identical thereto.

107. The method of claim 102 in which the reporter protein is DHFR, adenylate cyclase, or B-galactosidase.

108. The method of claim 102 in which the signal is a fluorescent signal.

109. The method of claim 102 in which the reporter protein is DHFR and the signal is detected by exposing the cells to fluorescence methotrexate, which can enter the cell and there bind to DHFR, rendering the cells fluorescent.

110. The method of claim 102 where the cells are subsequently subjected to fluorescence activated cell sorting.

111. The method of claim 102 where the receptor is the acetylcholine M2 muscarinic receptor.

112. The method of claim 102 where the reporter protein

is a constituitively active Ras protein mutant which is unable to localize to the cell membrane constituted there by the interaction of said first and second fusion proteins, and the signal is initially increased transcription on promoters containing AP-1 response elements.

113. The method of claim 112 where said cell further comprises a second reporter construct comprising a promoter with at least one AP-1 response element, said promoter operably linked to a second reporter gene.

114. The method of claim 102 in which the G alpha subunit is a Giα subunit.

115. The method of claim 102 where said reporter gene encodes a second reporter protein which is at least substantially identical to luciferase.

116. The method of claim 104 in which the cell is exposed to the substance before it is exposed to the known agonist.

117. The method of claim 104 in which the cell is exposed to the substance after it is exposed to the known agonist.

118. A method of identifying a substance as an agonist or antagonist of GPCR which comprises

(a) providing a cell which co-expresses

(i) a GPCR,

(ii) a G-alpha which binds said GPCR,

(iii) a first fusion protein comprising a donor fluorophore, and a first peptide which binds said G-alpha, and

(iv) a second fusion protein comprising either an acceptor fluorophore which is matched with said donor fluorophore for fluorescence resonance energy transfer, or a nonfluorescent acceptor which accepts fluorescence energy and thereby quenches from said donor fluorophore, and a second peptide which binds said G-alpha;

where one of said first and second peptides binds the G-alpha subunit in a substantially activation state-sensitive manner, and the other in a substantially activation state-insensitive manner;

(b) exposing said cell to said substance, thereby changing the level of activation of said G-alpha subunit,

where said first and second peptides bind said G-alpha subunit simultaneously if it is in the appropriate activation state;

said simultaneous binding resulting in a signal which is a fluorescence resonance energy transfer if the second fusion protein comprises an acceptor fluorophore, and is fluorescence quenching if said second fusion protein comprises a nonfluorescent acceptor, and

(c) detecting the change in the level of the signal.

119. The method of claim 118 in which the acceptor is a fluorophore.

120. The method of claim 118 in which the acceptor is not fluorescent.

121. The method of claim 118 in which the activation state-sensitive peptide is a T-peptide, so that if the substance is an agonist, it causes an increase in the signal, and if it is an antagonist, in a decrease in the signal.

122. The method of claim 118 in which the activation state-sensitive peptide is a D peptide so that if the substance is an agonist, it causes a decrease in the signal, and if it is an antagonist, in an increase in the signal.

123. A method of identifying a substance as an agonist or antagonist of GPCR which comprises

(a) providing a cell which co-expresses

(i) a GPCR,

(ii) a first fusion protein comprising a G-alpha subunit which binds said GPCR,

(iii) a second fusion protein comprises an activation state-specific peptide which binds said G-alpha subunit in the appropriate activation state,

where one of said fusion proteins comprises a donor fluorophore and the other comprises an acceptor,

and where said acceptor is either an acceptor fluorophore matched to the donor fluorophore for FRET, or a nonfluorescent

acceptor which quenches the fluorescence of the donor fluorophore,

(b) exposing said cell to said substance, so said substance can interact with said GPCR and thereby change the level of activation of said G alpha subunit moiety,

whereby, if the G-alpha subunit is in the appropriate activation state, said second fusion protein binds said first fusion protein, resulting in the interaction of said donor and acceptor to produce a signal, and

(c) detecting the change in the level of the signal as a result of said exposure of step (b).

124. A method of identifying a substance as an agonist or an antagonist of a receptor which comprises G protein coupled

(a) providing a cell which co-expresses

(i) said GPCR receptor,

(ii) a G-alpha subunit which binds with said receptor,

(iii) a fusion protein comprising a peptide which binds said G-alpha subunit in an activation state-specific manner, and a signalling protein moiety,

(b) exposing said cell to said substance, so it may interact with said receptor and thereby alter the level of activation of said G-alpha subunit, and thereby the level of recruitment of said fusion protein to the membrane,

said fusion protein, upon recruitment to the membrane, either activating a second, membrane-bound signalling protein, or becoming an active signalling protein itself, thereby resulting in a detectable signal,

(c) detecting the change in level of said signal as a result of said exposure.

125. A method of identifying a G-alpha subunit which interacts with a G-protein coupled receptor which comprises

(a) providing a library of cells, each cell coexpressing (i) GPCR and (ii) a chimeric G alpha subunit, said

chimeric subunits having different receptor-binding C-terminal but otherwise being substantially identical so as to participate in the same signalling pathway in said cell, said library collectively providing a plurality of different chimeric subunits representative of G alpha subunits with differing receptor specificities,

(b) exposing the cells to a known agonist of said GPCR,

(c) detecting the activation of the signaling pathway in one or more positive cells, and

(d) determining which chimeric G alpha subunit had been expressed in one or more of the positive cells.

126. In a method of identifying substances as agonists or antagonists of a G-protein coupled receptor, which comprises exposing a cell having such receptor to such substance and detecting a change in the level of activation of said receptor, said receptor interacting with a first G-alpha subunit, the improvement comprising

expressing in said cell a chimeric of said first G alpha subunit and a second G alpha subunit, said second G-alpha subunit participating in a different signaling pathway than the first unit, and detecting a change in the level of activation of the second signaling pathway.

127. The method of claim 126 in which the first G alpha subunit is Gq.

128. The method of claim 127 in which the second G alpha subunit is Gi.

129. The method of claim 127 in which the second G alpha subunit is Gi.

130. The method claim 126 where said cell expresses a plurality of different G alpha chimeras in which the first subunit varies but the second subunit is the same for each chimera.

131. The method of claim 126 wherein a library of cells is screened, said cells collectively expressing a plurality of different G alpha chimeras in which the first subunit varies but the second subunit is the same for each chimera.

132. In an assay to identify a substance as an agonist

or antagonist of a GPCR, in which a cell providing said GPCR is incubated with said substance, and the GPCR-mediated response of the cell to that substance is detected, the improvement comprising using, as a reagent, a peptide according to claim 86.

133. A method of determining whether a substance is an agonist or antagonist of a receptor of interest, where the co-activator of said receptor is unknown, which comprises (a) exposing said receptor to said substance; (b) further exposing said receptor to a plurality of oligomeric potential co-activators, each of which is a known co-activator of at least one receptor other than the receptor of interest; (c) if the substance is a suspected antagonist, further exposing, said receptor of interest to a known agonist thereof; and (d) determining whether there is a change in the level of activity of the receptor which is attributable to said substance.

134. The method of claim 133 where the receptor of interest is a nuclear receptor and the potential co-activators include a plurality of non-naturally occurring peptides each comprising an LXXLL motif.